

Trends in Fetal and Infant Survival Following Preeclampsia

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PREECLAMPSIA IS A WELL-known cause of perinatal mortality.^{1,2} Despite remarkable improvements in clinical management, preeclampsia often culminates in the delivery of a very preterm infant following medical intervention. Even mild preterm delivery substantially increases the risk of neonatal death.³ Therefore, when preeclampsia occurs early in pregnancy, even a few additional days in utero may be key to a newborn's survival.^{4,5} A review of clinical trials of delayed vs immediate delivery in fact suggested better outcomes with delayed delivery in well-selected patients.⁵ On the other hand, preeclampsia can progress rapidly, putting both mother and child at severe risk if no action is taken.

Medically indicated preterm delivery may help prevent stillbirth, as has been suggested for the United States.⁶ However, the infant might then pay a high compensatory price in postnatal increased risk. Such risk could persist well beyond the neonatal period but be difficult to detect on a population level because of the overall declining trend in infant mortality. Preeclampsia is a primary indication for preterm delivery in developed countries,⁷ a trend encouraged in part by the increasing ability to manage extremely preterm infants.⁵ For preeclampsia, the net effect of these changing medical prac-

Context Management of preeclampsia often culminates in induced delivery of a very preterm infant. While early termination protects the fetus from an intrauterine death, the newborn then faces increased risks associated with preterm delivery. This practice has increased in recent decades, but its net effect on fetal and infant survival has not been assessed.

Objective To assess the effect on fetal and infant survival of increased rates of early delivery of preeclamptic pregnancies.

Design, Setting, and Participants Population-based observational longitudinal study using registry data from 804 448 singleton first-born infants with Norwegian-born mothers and registered in the Medical Birth Registry of Norway between 1967 and 2003.

Main Outcome Measures Odds ratio (OR) of fetal and early childhood death in relation to preeclampsia.

Results Among preeclamptic pregnancies, inductions before 37 weeks increased from 8% in 1967-1978 to nearly 20% in 1991-2003. During this period, the adjusted OR for stillbirth decreased from 4.2 (95% confidence interval [CI], 3.8-4.7) to 1.3 (95% CI, 1.1-1.7) for preeclamptic compared with nonpreeclamptic pregnancies. During the same period, the OR for neonatal death after preeclamptic pregnancy remained relatively stable (1.7 in 1967-1978 vs 2.0 in 1991-2003). Later infant and childhood mortality also showed little change.

Conclusions Fetal survival in preeclamptic pregnancies has vastly improved over the past 35 years in Norway, presumably because of more aggressive clinical management. However, the relative risk of neonatal death following a preeclamptic pregnancy has not changed over time.

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tices on infant survival is important to assess. We examine changes over time in perinatal and early childhood survival in relation to preeclampsia in Norway.

METHODS

We used data from the Medical Birth Registry of Norway for the period from 1967 to 2003, linked with information from Statistics Norway. The Medical Birth Registry, initiated in 1967, records all births to Norwegian residents from the 16th week of gestation (from the 12th week since 1998). The recording of live births is 100% complete, while the ascertainment of stillbirths is virtually complete after the

22nd week of gestation. The midwife or attending physician at the delivery fills out the notification form for the registry.⁸

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We restricted this analysis to pregnancies of at least 24 weeks' duration and occurring in women who had themselves been born in Norway (93%). The latter restriction was to avoid potential confounding due to the increase over time of the proportion of births to foreign-born women (from 3%

in 1967 to 16.5% in 2003). We also excluded multiple births (2.5%) because these have also increased in frequency and because preeclampsia, preterm delivery, and perinatal death are all more frequent in multiple births.⁹

We further restricted the analysis to first births, thereby excluding pregnan-

cies in which the outcome of the previous pregnancy may have influenced medical management or the couple's decision to have another child.

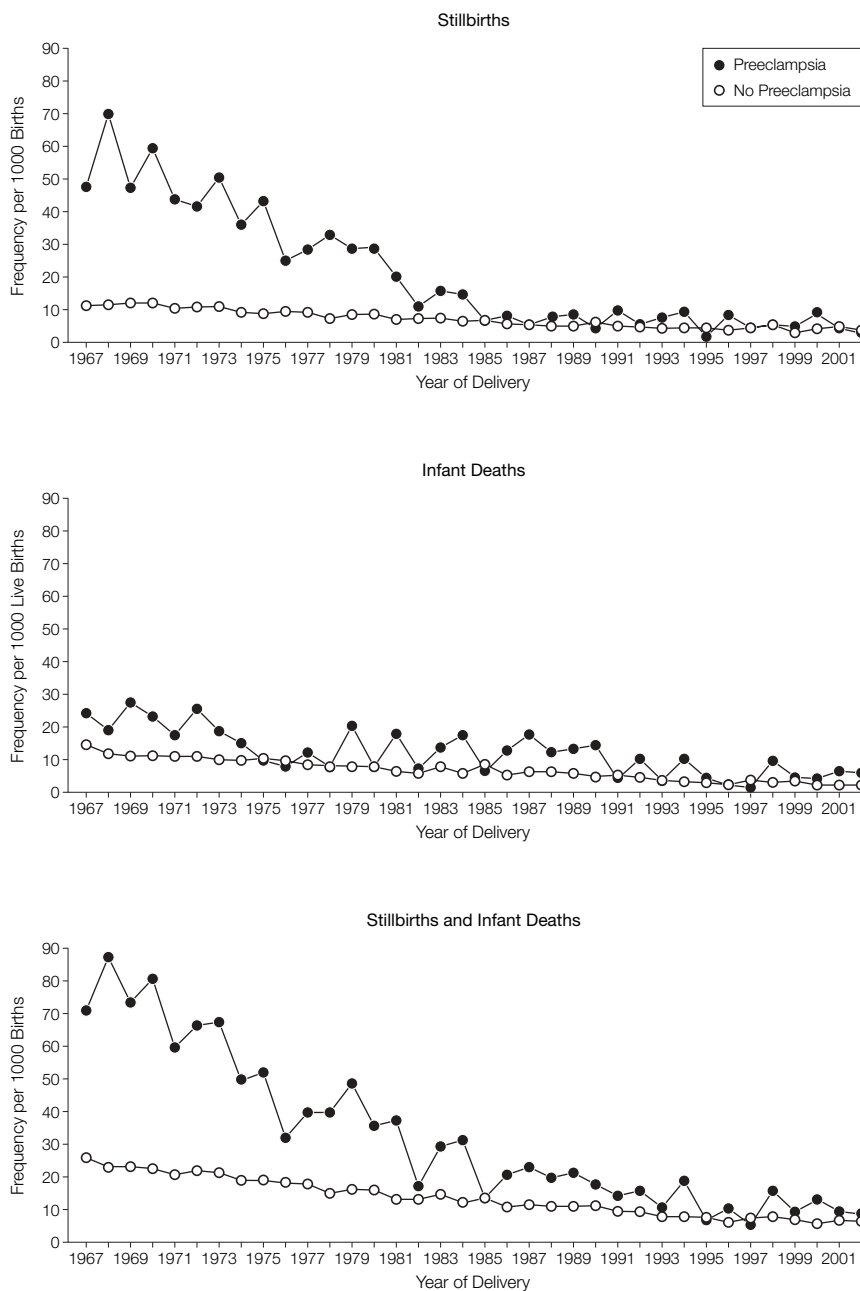
Of the 954 945 singleton births to Norwegian-born women entered for the first time in the registry, 797 127 (83.4%) were confirmed as first births by the maternal report. We excluded the 146 947 births for which the mother indicated a higher birth order, 90% of which occurred in the early phase of the registry (1967 to 1973). There were 10 871 women who delivered for the first time according to the registry, but for whom no maternal report of parity was recorded. We excluded 5 who delivered during the first 10 years of the registry; the remaining births were assumed to be first births.

We excluded 2330 infants born before the 24th completed week of gestation, according to the last menstrual period. Even though preeclampsia can be diagnosed from week 20, there were only 22 women who delivered between weeks 20 and 23 with a diagnosis of preeclampsia.

Gestational age calculated using last menstrual period was missing for 6.2%. Among these, we considered infants whose birth weight exceeded the 50th percentile (670 g) for 24 weeks in our data as "likely" to have been born at 24 weeks or later and therefore eligible for inclusion (thus excluding only 350 of the 49 033 infants with missing gestational age). We also excluded 865 infants for whom both gestational age and birth weight were missing. Among these 865, only 3 (0.3%) had a maternal diagnosis of preeclampsia and 8.3% died perinatally, suggesting that this group also included a high proportion of very preterm infants who would have been ineligible. These exclusions left a total of 804 448 infants for analysis.

Preeclampsia is reported to the registry as a specific diagnosis abstracted from the medical chart. The notification form contains information on signs, such as hypertension, proteinuria, and edema. In Norway, the diagnostic criteria for preeclampsia follow the 1972 recommendations of the American Col-

Figure 1. Changes in Fetal and Infant Mortality Between 1967 and 2002 in Norway as a Function of Preeclampsia



lege of Obstetricians and Gynecologists,¹⁰ which defined preeclampsia as increased blood pressure ($\geq 140/90$ mm Hg) after 20 weeks of gestation with proteinuria, edema, or both. In clinical practice, however, edema in the absence of hypertension and proteinuria will not lead to a diagnosis of preeclampsia. Diagnostic criteria have remained fairly constant since 1967.

In 1998 the notification form changed to permit a more detailed classification of preeclampsia. For the present analysis, however, preeclampsia was treated as a dichotomous outcome throughout. We used information from the birth registry to ascertain stillbirths and deaths up to 1 year, and from the cause-of-death registry for deaths in children aged 1 to 5 years.

We divided the births into 3 periods of roughly equal durations and numbers of births: 1967-1978, 1979-1990, and 1991-2003. We used logistic regression to estimate, separately for each period, the preeclampsia-related odds ratio for several end points: stillbirth, perinatal mortality (stillbirth plus death in the first 7 days of life), neonatal death (from day 1 to 28 among live births), and postneonatal death (from 29 to 365 days).

We had information on whether an infant had died during the first year of life only through 2003. Thus, when infant death was the outcome, we included only infants born through 2002.

Data on deaths beyond age 1 year were available through 2002. When we examined death between age 1 and 5 years, we included only children born through 2000. Using Cox regression, with age in months as the main time scale, children underwent follow-up until death, their fifth birthday, or December 31, 2002, whichever came first.

We adjusted the analyses for maternal age at delivery, mother's education, and mother's marital status at the time of birth. We chose these covariates based on their availability in the registry and because they are predictive of preeclampsia and also of stillbirth and childhood death. We did not

have data on prepregnancy body mass index (BMI), and information on smoking during pregnancy was only available from 1999 onward, so we were unable to adjust for either of these covariates.

We also fitted regression models for each outcome for the entire study period, with and without an interaction term between the period and preeclampsia. Our purpose was to test for differences in the estimated association between preeclampsia and mortality (stillbirth, infant death, stillbirth plus infant death, and death from age 1 to 5 years) across the 3 periods. To assess whether there was a significant interaction, we used the likelihood ratio test comparing the model that included the interaction term with the one that did not.

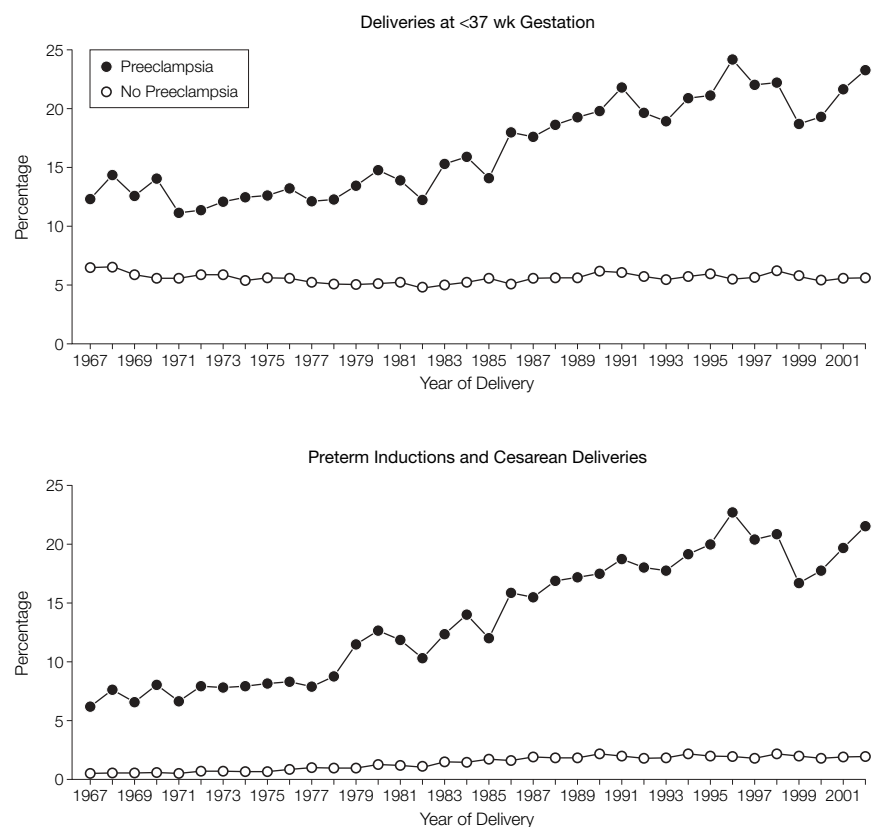
Research on anonymous registry data are routinely exempted from ethical review and informed consent requirements by the ethics research committees in Norway. This study was considered exempt by the National Institutes of Health institutional review board.

RESULTS

The analysis sample included 770 613 pregnancies without preeclampsia and 33 835 pregnancies with preeclampsia (4.2%).

As shown in FIGURE 1, stillbirth and infant death were both more frequent in preeclamptic pregnancies, especially in the early years. Stillbirth was much more strongly associated with preeclampsia, and improved more over time, than infant death. As shown in FIGURE 2, labor induction and cesar-

Figure 2. Changes in Preterm Induction Practice and Gestational Age Between 1967 and 2002 in Norway as a Function of Preeclampsia



Preterm inductions (including cesarean deliveries) are shown as a percentage of all births. Panels do not include records with a missing estimate of gestational age calculated using last menstrual period (6.1%).

Table 1. Outcomes of Preeclamptic and Nonpreeclamptic First Pregnancies, by Birth Period*

Outcome	No. (%)					
	1967-1978		1979-1990		1991-2003	
	No Preeclampsia (n = 275 815)	Preeclampsia (n = 8769) (3.1)	No Preeclampsia (n = 242 704)	Preeclampsia (n = 10 946) (4.3)	No Preeclampsia (n = 252 094)	Preeclampsia (n = 14 120) (5.3)
Death						
Perinatal death	4722 (1.71)	495 (5.64)	2303 (0.95)	193 (1.76)	1471 (0.58)	122 (0.86)
Stillbirth	2849 (1.03)	387 (4.41)	1601 (0.66)	130 (1.19)	1084 (0.43)	82 (0.58)
1-28 d†	2146 (0.79)	115 (1.37)	870 (0.36)	92 (0.85)	508 (0.20)	56 (0.40)
29 d-1 y‡	734 (0.27)	31 (0.37)	650 (0.27)	54 (0.50)	243 (0.10)§	20 (0.15)§
Stillbirth + infant death	5729 (2.08)	533 (6.08)	3121 (1.29)	276 (2.52)	1764 (0.75)§	150 (1.13)§
1-5 y	625 (0.23)	19 (0.23)	399 (0.17)	26 (0.24)	172 (0.09)	11 (0.10)
Birth						
Before 37 wk	15 337 (5.77)	1056 (12.55)	12 052 (5.35)	1639 (16.34)	13 184 (5.66)	2744 (21.09)
Before 32 wk¶	3083 (1.16)	134 (1.59)	2127 (0.94)	299 (2.98)	2156 (0.93)	654 (5.03)
Cesarean delivery	10 142 (3.68)	1438 (16.40)	25 846 (10.65)	3876 (35.41)	31 711 (12.58)	5257 (37.23)
Induction#	29 871 (10.83)	2591 (29.55)	25 873 (10.66)	2832 (25.87)	23 384 (9.28)	5009 (35.47)
Induction + cesarean delivery before 37 wk**	1585 (0.60)	638 (7.59)	3501 (1.55)	1428 (14.23)	4410 (1.89)	2519 (19.36)

*Restricted to deliveries from 24 completed weeks of gestation onward.

†The denominator includes only live births.

‡The denominator includes only infants surviving beyond the 28th day of life.

§Only infants born through 2002 are included (233 778 and 13 108 without and with preeclampsia during pregnancy, respectively), as death information for 2004 is incomplete.

||Only infants born through 2000 are included for this period (199 490 and 10 774 without and with preeclampsia during pregnancy, respectively; censoring is not considered in the calculation).

¶Only infants with gestational age calculated using last menstrual period are included. The numbers missing gestational age, without and with preeclampsia during pregnancy, are 9845 and 358, respectively, for 1967-1978; 17 258 and 914 for 1979-1990; 19 197 and 1111 for 1991-2003.

#If a woman had both an induction and a cesarean delivery, she is counted among the cesarean deliveries only.

**Inductions and cesarean deliveries performed before 37 weeks out of all births (see ¶ footnote for number of births with missing gestational age).

Table 2. Crude and Adjusted Risk of Death as a Function of Preeclampsia, by Birth Period*

Outcome	OR (95% CI)		
	1967-1978	1979-1990	1991-2003
Crude Risk			
Perinatal death	3.44 (3.12-3.78)	1.87 (1.62-2.17)	1.49 (1.23-1.79)
Stillbirth	4.42 (3.97-4.93)	1.81 (1.51-2.17)	1.35 (1.08-1.69)
Death 1-28 d†	1.76 (1.45-2.12)	2.37 (1.91-2.94)	1.98 (1.50-2.60)
Death 29 d-1 y‡	1.39 (0.97-1.99)	1.87 (1.41-2.46)	1.47 (0.93-2.32)§
Stillbirth + infant death	3.05 (2.78-3.34)	1.99 (1.75-2.25)	1.52 (1.28-1.79)§
Death 2-5 y (HR)	1.00 (0.63-1.57)	1.46 (0.98-2.18)	1.20 (0.65-2.21)¶
Adjusted Risk#			
Perinatal death	3.32 (3.01-3.65)	1.86 (1.60-2.15)	1.48 (1.23-1.78)
Stillbirth	4.21 (3.77-4.69)	1.79 (1.49-2.14)	1.34 (1.07-1.68)
Death 1-28 d†	1.74 (1.44-2.11)	2.37 (1.91-2.94)	1.98 (1.50-2.61)
Death 29 d-1 y‡	1.39 (0.97-1.99)	1.88 (1.42-2.48)	1.48 (0.94-2.33)§
Stillbirth + infant death	2.96 (2.70-3.25)	1.98 (1.74-2.24)	1.51 (1.28-0.79)§
Death 2-5 y (HR)	1.01 (0.64-1.59)	1.47 (0.99-2.19)	1.20 (0.65-2.21)¶

Abbreviations: CI, confidence interval; HR, hazard ratio (see below); OR, odds ratio.

*Restricted to deliveries from 24 completed weeks of gestation onward.

†The denominator includes only live births.

‡The denominator includes only infants surviving beyond the 28th day of life.

§Only infants born through 2002 are included (233 778 and 13 108 without and with preeclampsia during pregnancy, respectively), as death information for 2004 is incomplete.

||Hazard ratio from Cox regression, with age in months as the time scale.

¶Only infants born through 2000 are included for this period. Censoring is taken into account in the model.

#Adjusted for mother's age (≤ 19 , 20-24, 25-29, 30-34, and ≥ 35 years), civil status (married or cohabiting, not married or cohabiting, other), mother's education (no high school, high school, beyond high school, missing information [0.3%]).

ean deliveries prior to 37 completed weeks of gestation increased throughout the study period for both pree-

clamptic and nonpreeclamptic pregnancies but were about 10 times as likely to be performed in preeclamptic preg-

nancies. Despite more interventions, the rate of preterm delivery among non-preeclamptic pregnancies remained stable over time. However, it increased substantially in preeclamptic pregnancies. The dramatic decline in stillbirths associated with preeclampsia seems to have begun a few years prior to the increase in the rate of early termination of preeclamptic pregnancies.

TABLE 1 divides the data into the 3 periods. The incidence of recorded preeclampsia in singleton first births increased from 3.1% in 1967-1978 to 5.3% in 1991-2003. The incidence of stillbirth was halved from the earliest to the latest period among nonpreeclamptic pregnancies, while it was reduced more than 7-fold among preeclamptic pregnancies. An increase in preterm delivery was evident, with a tripling of deliveries before 32 weeks. In the period from 1991 to 2003, more than 90% of preeclamptic preterm births resulted from induction or cesarean delivery, compared with about 60% in 1967-1978. Among preterm

deliveries the percentages associated with preeclampsia were 6%, 12%, and 17% in the 3 periods, respectively. The mean gestational age at birth among nonpreeclamptic pregnancies decreased very slightly, from 282.1 days in 1979-1990 to 281.6 in 1991-2003, while among preeclamptic pregnancies it decreased from 277.1 days in 1967-1978, to 274.2 in 1979-1990, and to 270.8 in 1991-2003.

TABLE 2 reports the estimated odds ratios of death (categorized in several ways) after preeclampsia for the 3 periods. In 1967-1978 there was a much higher risk of death among preeclamptic pregnancies than among nonpreeclamptic ones, especially for stillbirth. This excess risk declined substantially over time. We saw no analogous improvement for postnatal death.

We tested for differences in the association between preeclampsia and death among the 3 periods for different categories of mortality. The excess mortality due to preeclampsia decreased significantly over time for stillbirth and stillbirth plus infant death ($P < .001$), while for neonatal, infant, and childhood mortality there was no statistical evidence of change in the excess risk across the 3 periods ($P > .05$ for all).

COMMENT

Offspring from preeclamptic first births in Norway had a higher risk of fetal and infant death than did offspring from nonpreeclamptic first births. Over the 37 years examined, survival following preeclampsia improved largely through a substantial reduction in stillbirths, most likely as a result of improvements in clinical management and well-targeted medical intervention. Early termination of pregnancy would be expected to lower the risk of stillbirth in part by truncating the fetal time at risk, and a decrease in stillbirths did occur in Norway. Potentially, a fetus at risk of stillbirth who is delivered early could instead die soon after birth. Nonetheless, despite the increase in premature deliveries of preeclamptic pregnancies,

there was no offsetting increase in neonatal mortality, presumably reflecting general improvements in the neonatal care of preterm infants over time. In 1967-1978, more than 25% of all infants born before 34 completed weeks died in the neonatal period, as opposed to 5% in 1991-2003. We cannot, however, rule out the possibility of an increase in infant or childhood morbidity resulting from very preterm delivery, as we cannot address this aspect with the current data.

This study was based on a large data set spanning more than 3 decades, with complete ascertainment of deaths occurring after birth and virtually complete ascertainment of stillbirths.⁸ The definition of preeclampsia remained substantially unchanged during the study period; specifically, medical practice in Norway would not diagnose as preeclamptic women with hypertension and edema in the absence of proteinuria.¹¹ The increase in preeclampsia over time may reflect increases in BMI in recent years,¹² and it may also indicate improved reporting over time. The change in 1998 to reporting to the Medical Birth Registry starting with the 12th week of gestation may have contributed (together with improved prenatal surveillance) to more complete reporting of mild preeclampsia, which could partly explain the observed improvement in outcomes. However, the decline in stillbirths was too strong to be entirely explained by possible trends in diagnostics. Excluding births from 1998 (when the notification form was revised) and onward yielded a similar estimate for stillbirth in 1991-2003 (odds ratio, 1.43 instead of 1.34).

Prenatal care has been universally available in Norway throughout the study period, and preeclampsia is easily diagnosed by screening methods that are routine and noninvasive. Early diagnosis of preeclampsia depends chiefly on how early the woman receives prenatal care and less so on the diagnostic tools. While there is no evidence that women are getting prenatal care earlier, our analysis suggests that action is

being taken earlier in pregnancy, as reflected by the increasing fraction of preterm deliveries of preeclamptic pregnancies. We did not have information on the gestational week of diagnosis of preeclampsia. However, even if preeclampsia has been diagnosed earlier in recent years (thus leading to more complete ascertainment among women delivering preterm), such a change in classification could not plausibly explain the marked increase over time in the rate of preterm deliveries among preeclamptic pregnancies.

We lacked data on potentially important confounders, such as BMI and maternal smoking, which are associated with both preeclampsia and mortality. Smoking information has been recorded since 1999, and the registry does not record BMI. Education and marital status may serve as partial proxies for these factors, because married or cohabiting couples had a higher risk of preeclampsia (possibly reflecting a lower prevalence of smoking) than noncohabiting couples, whereas higher education (which may correlate with lower BMI) was negatively associated with preeclampsia. Understandably, the associations with these factors were weaker than those expected for BMI and smoking. Nevertheless, adjustment for these covariate proxies had virtually no impact on the estimates, even though they were associated with both preeclampsia and death. Smoking during pregnancy, which is protective for preeclampsia,¹³ declined in Norway during the study period. One survey reported a decline from 32% in 1970 to 27% in 1991.¹⁴ According to another survey, smoking declined from 34% in 1987 to 22% in 1994.¹⁵ This trend may have contributed slightly to the observed increase in the rate of preeclampsia and to the decline in stillbirth and infant death.

We did not adjust for either gestational age or birth weight in these analyses. Preeclampsia causes early delivery (either spontaneous or through medical intervention), and timing of delivery is associated with mortality risk. Thus, gestational age is caused in part

by the exposure and should not be treated as a confounder. Adjusting for it could, in fact, produce bias.^{16,17} Similarly, analyses should not include adjustment for birth weight, as it is part of the same causal pathway.

The data we examined were specific for Norway, and conclusions cannot necessarily be extended to other countries. It is likely, however, that industrialized countries with a similar level of obstetric intervention and facilities for treating very premature infants would show a similar pattern.

While our data strongly suggest that medical interventions in the management of preeclampsia have benefited the fetus (and, presumably, the mother), these results do not per se imply that early interruption of pregnancy is justified; factors other than early termination have probably contributed as well. The fact that the decline in stillbirths seems to have preceded the increase in early termination of preeclamptic pregnancies suggests that some improvements in fetal survival

may have been due to other changes in the clinical management of preeclampsia. Much of the favorable trends we have documented in Norway may be due to careful use of fetal monitoring to inform those clinical choices and to the use of corticosteroids to accelerate lung maturation in preterm infants.⁴ Physicians face a real dilemma in balancing the risk of fetal/neonatal/maternal death due to preeclampsia against the increased risk of death associated with preterm delivery. Our data suggest that, in Norway at least, all these decisions have worked to the net advantage of the child, while achieving a low maternal mortality rate.¹⁸

In summary, preeclampsia was an important cause of fetal death in Norway during the late 1960s and throughout the 1970s, but its impact has waned. While risk of stillbirth was 4.2 times higher with preeclampsia, it is now only 1.3 times higher. Preeclampsia still carries a 2-fold increased risk of neonatal death, which has changed little over time. This stability in neonatal risk is remarkable, considering the increas-

ing number of very preterm deliveries in recent years resulting from aggressive obstetric management of preeclampsia. Modern medical management of preeclampsia appears to have been effective in preventing fetal death without causing an increase in infant or maternal death.

Author Contributions: Dr Basso had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Basso, Rasmussen, Weinberg, Wilcox, Irgens, Skjaerven.

Acquisition of data: Irgens, Skjaerven.

Analysis and interpretation of data: Basso, Rasmussen, Weinberg, Wilcox, Irgens, Skjaerven.

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Critical revision of the manuscript for important intellectual content: Basso, Rasmussen, Weinberg, Wilcox, Irgens, Skjaerven.

Statistical analysis: Basso, Rasmussen, Weinberg, Irgens, Skjaerven.

Administrative, technical, or material support: Irgens, Skjaerven.

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public. Failure of authors to disclose as required indeed “does not automatically translate to the article being flawed.”¹ Nevertheless, it does create the perception that the authors had something to hide and decreases public trust in medical research.

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3. The Federation of American Societies for Experimental Biology (FASEB). News FASEB: July 14, 2006. <http://opa.faseb.org/pdf/LeoFurchtPresident7.14.06.pdf>. Accessed October 24, 2006.

In Reply: It is very encouraging to know that a prestigious organization such as FASEB has developed principles and standards for conduct and management of academia-

industry interactions from the scientists' perspective. It will take such initiatives by scientists, industry, journals, and all others involved in discovery and dissemination to assure public trust in biomedical science.

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CORRECTIONS

Incorrect Data and Omission of Trial Site and Personnel: In the Original Contribution entitled “Effects of Tamoxifen vs Raloxifene on the Risk of Developing Invasive Breast Cancer and Other Disease Outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial” published in the June 21, 2006, issue of *JAMA* (2006;295:2727-2741), incorrect data were reported. In Table 2 on page 2731, the risk ratio (RR) for estrogen receptor-positive patients should have been reported as 0.94, not 0.93; in the “Invasive Breast Cancer” panel of Figure 2 on page 2732, the number at risk in the raloxifene group at 36 months should have been reported as 6702, not 6701; and in Table 5 on page 2735, the rate per 1000 for ischemic heart disease in the tamoxifen group should have been reported as 2.99, not 3.00, and the difference between the rates by treatment group should have been reported as -0.30, not -0.29. Also, a trial site and its personnel were inadvertently omitted: in the list of active NSABP STAR P-2 clinical centers appearing on page 2739, “Boston Medical Center, Boston, Mass: Marianne N. Prout (PI), Liz Pottier (PC);” should have appeared between the entries for Boca Raton Community Hospital and CAMC Health Education and Research Center.

Incorrect Terminology: In the Original Contribution entitled “Trends in Fetal and Infant Survival Following Preeclampsia” published in the September 20, 2006, issue of *JAMA* (2006;296:1357-1362), the term “risk” was incorrectly used in Table 2 on page 1360. The Table 2 title should have read “Crude and Adjusted Odds Ratios [rather than risk] for Death as a Function of Preeclampsia, by Birth Period.” Similarly, the cut-in headings in the table should have read simply “Crude” and “Adjusted.”